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EXAMINER

VOGEL, NANCY S

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**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Application Number: 09/834,424
Filing Date: April 13, 2001
Appellant(s): SCHREIBER ET AL.

Charles E. Lyon
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 10/2/06 appealing from the Office action
mailed 7/15/05.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The following are the related appeals, interferences, and judicial proceedings known to the examiner which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal:

An Appeal Brief has been filed in U.S. Serial No. 09/430,508, that addresses some issues that overlap with the issues presented here.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Wold, "Bifunctional Reagents", Methods in Enzymology, Vol.11 (1966), pages 617-640

Art Unit: 1636

Ji, "Bifunctional Reagents", Methods in Enzymology, Vol. 91 (1993), pages 58-609

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This rejection is based on the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. §112, first paragraph "Written Description" Requirement published in the Federal Register (Volume 66, Number 4, pages 1099-1111). Claim 8 is drawn to a method for preparing an agent that effects a biological event mediated by the association of two or more endogenous cell surface receptors, the method comprising preparing said agent which includes a first non-peptidic moiety that binds to one of the cell surface receptors covalently linked to a second non-peptide moiety that binds to the other cell surface receptor, wherein the agent binds to both cell surface receptors. Claim 19 is drawn to a method for preparing an agent that effects a biological event mediated by the association of two or more endogenous protein

Art Unit: 1636

mediators, the method comprising preparing an agent which includes a first non-peptide moiety that binds to one of the protein mediators covalently linked with a second non-peptide moiety that binds to the other protein mediator, wherein the agent binds to both protein mediators, the biological event is mediated by the association of molecules of two different protein mediators and the first and second moieties are different. These are genus claims in terms of any methods of preparing any agent made up of two non-peptidic moieties that has the ability to bind two cell surface receptors (claims 8-18) or two endogenous protein mediators (claims 19-29) in order to effect a biological event.

The specification specifically mentions several possible agents such as immunophilins (i.e. FK506 or rapamycin) and other ligands that bind to a receptor or binding partner, and further state that "other compounds capable of binding to those receptors or to other endogenous constituents may be readily identified using a variety of approaches" (page 14, lines 12-13 of the specification). None of these moieties have been shown, when combined with a second non-peptidic moiety, to effect a biological event, and therefore it is unclear that these "dimerizers" will serve to actually activate a signal transduction/biological event by dimerizing their targets. Thus, there is no description of even a single compound that is comprised of two non-peptidic moieties that each bind to a cell surface receptor, or endogenous protein mediator, where the agent can effect a biological event mediated by the association of the two receptors or endogenous protein mediators. Therefore, the description provided by the specification is not deemed to be descriptive of a structure-function relationship of a representative number of species that are encompassed by the claims. This is because the skilled

artisan cannot envision a sufficient number of agents which include two non-peptide moieties that bind to cell surface receptors or endogenous protein mediators, wherein the compounds have the ability to effect a biological event mediated by the association of the two cell surface receptors or endogenous protein mediators. There is no description of a structural feature that correlates with the functional ability of an agent to bind two cell surface receptors, or two endogenous protein mediators in a manner which results in an effect on a biological event mediated by the association of said receptors or endogenous protein mediators. Irrespective of the fact that such disclosed agents as immunophilin-based agents are questionable with respect to their functionality in the claimed invention, there is not even a disclosure that the immunophilin-based agents are representative of all agents within the genus of compounds that are effective to bind to two receptors or endogenous protein mediators in a manner effective to elicit an effect on a biological event. As a result, the instant specification does not describe the method for preparing agents which effect a biological event in such a clear and concise manner so as to indicate that the appellant had possession of these agents at the time of filing of the application. Thus the written description requirement has not been satisfied.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

Art Unit: 1636

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 8-16 and 18-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Wold (Methods in Enzymology Vol. 11, pages 617-640, 1966).

Wold disclose methods of preparing agents comprising preparing an agent which includes a first non-peptidic moiety that binds to one cell surface receptor covalently linked to a second non-peptide moiety that binds to the other cell surface receptor, wherein the agent binds to both cell surface receptors (see page 618, lines 17-28; see pages 622 line 34 – page 640). The two moieties may be the same or different (see page 618, last paragraph). The reference discloses the method of preparing bifunctional reagents whose molecular weight of the first and second non-peptide moieties are less than 5 Kd (see for example page 623, 625, 627). In the absence of evidence to the contrary, the agents disclosed by Wold would bind to any two proteins, including cell surface receptors, or two endogenous protein mediators, which are in physical proximity, thereby effecting a biological function.

Claims 8-29 are rejected under 35 U.S.C. 102(b) as being anticipated by Ji et al. (Methods in Enzymology, Vol. 91, pages 580-609, 1983).

Ji et al. disclose methods of preparing agents comprising preparing an agent which includes a first non-peptidic moiety that binds to one cell surface receptor covalently linked to a second non-peptide moiety that binds to the other cell surface receptor, wherein the agent binds to both cell surface receptors, including such agents as formaldehyde and gluteraldehyde, which form polymeric forms in solution and which bind and cross-link membrane proteins or other proteins nonspecifically (see page 601-

602). The reference discloses formaldehyde and glutaraldehyde in aqueous solutions (see page 602). The reference discloses that some reagents are permeant to membranes (page 581). The reference discloses preparation of bifunctional reagents, having two different moieties which each can bind to any protein of interest (see page 584, second complete paragraph through page 601). The reference discloses the method of preparing bifunctional reagents whose molecular weight of the first and second non-peptide moieties are less than 5 Kd (see for example pages 591 and 592). In the absence of evidence to the contrary, it is considered that the agents disclosed by Ji would bind to any two proteins, including cell surface receptors, or two endogenous protein mediators, which are in physical proximity, thereby effecting a biological function.

(10) Response to Argument

Appellant's arguments set forth in the Appeal Brief filed 10/2/06 have been considered but have not been found convincing.

The rejection under 35 USC 112 p. 1, Written Description

Appellant is claiming the ability to prepare an agent that effects a biological event mediated by the association of any two or more endogenous cell surface receptor molecules, wherein the agent comprises any first non-peptidic moiety that binds to one of the cell surface receptor molecules covalently linked to a second non-peptidic moiety that binds to the other cell surface receptor molecule, wherein the agent binds to both cell surface receptor molecules. Appellant first argues that "the relevant biological events necessarily occur whenever the appropriate proteins are associated". Appellant

Art Unit: 1636

cites Spaargaren et al. for support for this argument. However, is maintained, as was maintained previously, that while references may be found which show that biological events occur in some cases of some receptors when they reacted with bivalent antibodies, this citation of particular receptors and antibodies does not support appellant's assertion that any and all agents that bind to a receptor, necessarily trigger a biological effect. Appellants provide a quote from Austin et al., as they did previously in the response of 4/25/05. However, the quote set forth in page 10 of the Appeal Brief simply speculates that one can create dimerizers with "tailor made properties" that "simply create a high local concentration of a particular protein at a particular cellular location". There is no statement, implicit or explicit, in the quotation supplied in the Appeal Brief, that the mere association of receptors by any agent, would necessarily result in effecting a desired biological event. Even if one were to accept that the mere binding of an oligomerizing agent to a receptor was sufficient to activate a signal cascade, this does not rectify the fact that the specification fails to meet the Written Description requirement. This is because the issue concerning the Written Description rejection involves the identity of agent-receptor combinations. Appellants cannot point to anywhere in the instant specification indicating where these agent-receptor combinations are described. Appellants' only support in the art comes from post-filing references, where entirely novel compounds (i.e., agents which are not contemplated at all in the instant specification) had to be discovered in order to practice a very small scope of the claimed invention. The fact that binding and effecting are considered equivalent by Appellant does not remedy this situation.

Appellant further argues that 3 factors set forth by the court in *Noelle v. Lederman*, 355 F. 3d 1343 (Fed. Cir. 2004), establishing that when an antigen is fully defined, the antibody is also described, are applicable in this case (pages 11-15).

Appellant states that in *Noelle*, it was held that as long as applicant has a fully characterized antigen, the applicant can claim an antibody by its binding affinity to that described antigen. The three factors to support this conclusion are set forth as: the well defined structural characteristics for the five classes of antibody, the functional characteristics of antibody binding, and the fact that antibody technology is well developed and mature (page 11). Appellant goes on to argue that there are strong parallels between the present situation and the antibody case addressed in *Noelle*.

Regarding the first factor, Appellant argues that the court in *Noelle* would allow claims to the genus of antibodies without the applicant having made them, or envisioned the chemical structure (page 12), and that therefore by analogy, in the instant case, the precise chemical structures of the non-peptidic moiety and receptor molecules to which they bind and activate, are not required for a complete written description. Regarding the second factor, Appellant argues that the relevant "functional characteristics" in *Noelle* were the ability of antibodies to bind to a known antigen, and in the instant case, it is the ability of the "dimerizing" non-peptidic agents to bind to a known target (page 12). Regarding the third factor, Appellant argues that in the instant case, like the antibody technology of *Noelle*, "[t]echnologies for identifying non-peptidic agents that bind to a given target were well established at the time the present application was filed" (pages 12-13). Appellant lists several articles that disclosed that "combinatorial libraries

Art Unit: 1636

of agents were being developed” and “[a] whole host of binding assays for screening these diverse agents were also known” and “high-throughput screening systems for identification of binding agents were being used”.

In response, it is maintained that the instant case facts are not similar or analogous to the facts in *Noelle*. In the instant case, Appellant is attempting to describe non-peptidic compounds, while in *Noelle*, the court considered under what conditions it would be considered that antibodies directed against a particular antigen would be fully described. The difference between these fact situations is clear: antibodies are large proteins having well-defined structures. In the instant case, the genus of “non-peptidic moiety” encompasses a huge universe of molecules having no structural limitation other than they do not contain peptides, i.e. they are not proteins. This is a huge qualitative and quantitative difference from the facts of *Noelle*. Importantly, it is well established that to make an antibody, you only need to be in possession of the antigen, since by putting the antigen into an animal, you create an immunogenic reaction that will *necessarily* result in the production of an antibody. Appellant appears to be certain that there are many oligomerizing non-peptidic agents for every receptor that acts through an oligomerization event, without indicating where they describe these agent-receptor binding pairs in their specification. It is unclear how Appellant can unequivocally state that there are multiple oligomerizing agents for any given receptor. It is again maintained that, if the skilled artisan must experimentally determine or discover the very nature of the invention (i.e. what agents must be

Art Unit: 1636

prepared to practice the invention), the Written Description requirement cannot be satisfied.

Appellants argue that the technologies for identifying small molecule ligands that bind to a given target were well established at the time the present application was filed, and cites references disclosing such methods as combinatorial library screening, and high-throughput screening systems (pages 12-13). While it is acknowledged that such techniques of discovery have been known in the art, the desire to isolate new and useful compounds does not constitute a description of such compounds. *Vas-Cath V. Mahurkar*, 19USPQ2d 1111, clearly states “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the ‘written description’ inquiry, *whatever is now claimed*.” (See page 1117). The specification does not “clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is now claimed.” (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of agents which will bind to two cell surface receptors in a manner which results in an effect on a biological event mediated by the association of said receptors, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation or identification. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required.

Evidence has been submitted showing that other groups (Qureshi and Tian) have isolated such substances (page 15), in order to support the argument “only a small number of specific examples (only one!) is required to describe the present invention to those of ordinary skill in the art” (page 15). However, it is unclear how the success of other researchers, after the date of filing in the instant application, in discovering agents that function to bind to cell receptors, is sufficient to provide a written description of the genus of methods for preparing agents that effect a biological event mediated by the association of two or more endogenous cell surface receptor molecules comprising preparing a agent which includes a first non-peptidic moiety that binds to one of the cell surface receptor molecules covalently linked to a second non-peptide moiety that binds to the other cell surface receptor molecule, wherein the agent binds to both cell surface receptor molecules. Appellant has provided no specific description in the instant specification concerning which agent-receptor combination should be prepared in the claimed method. The agent-receptor combination is the key operable element to the claim, as a biological event cannot be effected in the claimed manner unless the skilled artisan knows which agent to prepare. It is clear that the structures of agents to be prepared in the claimed method are not disclosed in the instant specification; the post-filing teaching of Qureshi and Tian shows that the structures which have the claimed function were not described in the instant application. While virtually limitless numbers of structures of non-peptidic moieties are known, the particular non-peptidic moiety which possesses the structure to fulfill the recited

Art Unit: 1636

functions (i.e. two covalently linked non-peptidic moieties that bind to a particular cell surface receptor and effect a biological event) are not known.

Describing a structure-function relationship is the nature of Written Description, thus the Examiner is not being overly rigid but rather applying the appropriate standards. It is not simply enough to say that an agent must bind to the receptor it is designed to oligomerize in order to establish a structure-function relationship. There must be a particular structure(s) that is disclosed to bind to a particular receptor-type such that the skilled artisan could envision that agents having the structure(s) could be used to oligomerized the particular receptor-type, thereby effecting a biological function. The wish or desire to isolate appropriate binding moieties is not sufficient.

Appellant has maintained that each of the following individual or groups of claims stand or fall together: 8, 19, 9, 12, 20, 21, 29; 10; 11; 18; 13; 14; 15; 16; 17; 22-24; 25-26; and 27, apparently for the reason that each of the groupings recite a smaller "universe of receptors" than the first grouping, i.e. claims 8, 19, 9, 12, 20,21 and 29. Appellant argues that "the level of description in the specification required would be reduced as compared with claim 8" in the groups wherein specific receptors are recited (page 16-18). However, it is maintained that the same reasons for maintaining the rejection under 35 USC 112 p.1, written description, applies to those claims in which a specific receptor(s) apply, since the universe of agents from which a specific agent is to be selected to be prepared are equally large, and the particular agent is equally unknown and not described, for particular receptors, as they are for the entire genus of

Art Unit: 1636

non-specified receptors. Therefore, the reasons set forth above for maintaining the rejection apply to all of the claims and groups of claims.

The rejection under 35 USC 102(b) in view of Wold

Appellants has argued that Wold do not disclose methods that involve an agent that "*binds* non-covalently to two or more endogenous protein mediators. Instead, Wold teaches bifunctional reagents that *react with* and therefore form *covalent* bridges within or between proteins" (page 19 of the Brief). Appellant maintains that such covalent bonds are not encompassed by the claim language, which recites that the agent "binds to one of the cell surface receptor molecules". However, it is maintained that there is no such limitation in the claims to exclude covalent binding of the agent to the cell surface receptor molecules; contrary to applicant's arguments, the term "binds" does not exclude covalent binding. Appellant argues at pages 19-20 that the "broadest reasonable interpretation" of the claims must also be consistent with the interpretation that those skilled in the art would reach. Appellant points to sections in the specification where it is stated that binding affinities should be of a K_d below about 10^{-6} , and further recites that it is preferably below about 10^{-7} , 10^{-8} , or 10^{-9} , and that therefore one would know that covalent bonds were not encompassed. However, it is maintained that this description does not eliminate those compounds which would form a stronger bond, i.e. covalent bonds, especially since a range of affinities, which has no lower (stronger) limit is disclosed. Furthermore, appellant argues that since the specification and claims recite the terms "covalently linked", "covalently joined" and "covalently attached" to refer

Art Unit: 1636

to the bond between the first and second non-peptidic moieties of the agent, "[a] skilled person would appreciate that this further differentiates the claim term "binds" from covalent bonding" (page 20). However, such an implication is not clear. The lack of the recitation of the type of "binding" intended in the case of the bond between the agent and the receptor, is the only relevant issue, not whether the term "covalent" is used for the bond between the first and second non-peptidic moiety. Since the covalent type of bond is a reasonable interpretation in the claims, it is maintained that the art cited applies and the rejection is maintained.

Regarding whether Wold anticipates claim 17, the rejection of this claim under Wold has been withdrawn.

The rejection under 35 USC 102(b) in view of Ji

This rejection is maintained essentially for the reasons made of record in the previous Office action, mailed 11/2/04.

Appellant has responded to the rejection over Ji with identical arguments as those set forth for the rejection over Wold, and therefore the same reply applies. Applicants has argued that Ji does not disclose methods that involve an agent that "binds non-covalently to two or more endogenous protein mediators. Instead, Ji teaches bifunctional reagents that *react with* and therefore form *covalent* bridges within or between proteins" (page 22 of the arguments). Applicant maintains that such covalent bonds are not encompassed by the claim language, which recites that the agent "binds to one of the cell surface receptor molecules". However, it is maintained

Art Unit: 1636

that there is no such limitation in the claims to exclude covalent binding of the agent to the cell surface receptor molecules; contrary to applicant's arguments, the term "binds" does not exclude covalent binding. Furthermore, it is maintained that Ji does disclose that certain cross-linking agents are membrane permeable (page 581), and furthermore, the reference discloses agents such as formaldehyde and gluteraldehyde in aqueous solutions which may be considered a pharmaceutically acceptable excipient (see page 602). Therefore, the rejection is maintained.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.


Respectfully submitted,

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